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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,273	01/05/2007	Mathew James Francis	048501/311532	1951

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EXAMINER	
METZMAIER, DANIEL S	

ART UNIT	PAPER NUMBER
1796	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,273	FRANCIS ET AL.	
	Examiner	Art Unit	
	Daniel S. Metzmaier	1796	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/10/2007 & 6/11/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 May 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/10/2007 & 6/11/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending.

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

2. The information disclosure statement filed 10 May 2007 (foreign reference no. 2) and 11 June 2009 (Foreign references no. 16, 17, 18 and 19) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. For applicants' convenience, the references are cited on the PTO-892.

No copies of the above noted references were found in the Official record.

Drawings

3. The drawings are objected to because they do not comply with 37 CFR 1.84(u)(1).

> (u) Numbering of views.
> (1) The different views must be numbered in consecutive Arabic numerals, starting with 1, independent of the numbering of the sheets and, if possible, in the order in which they appear on the drawing sheet(s). Partial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter. **View numbers must be preceded by the abbreviation "FIG."** Where only a single view is used in an application to illustrate the claimed invention, it must not be numbered and the abbreviation "FIG." must not appear.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

4. The disclosure is objected to because of the following informalities: the status of the parent US applications should be updated to provide their latest pending status, *e.g.*, ", pending", ", abandoned" or ", now US (insert Pat No.), issued (insert date or issue)".

The reference to the figures should correspond to the figure labels, *e.g.*, Fig. 1, Fig. 2, etc., at all occurrences. See above drawings objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8, 12 and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 17 are indefinite regarding at what point in the process the agent is a solid. In claim 17, it is unclear if applicants intend a dispersed solid.

Claim 12 is indefinite because it is unclear what is the dispersed phase and what is the phase that is dispersing the dispersed phase. Claim 12 sets forth: "A dispersion of droplets of a liquid or oily hydrophobic pharmaceutically active agent, or a hydrophobic pharmaceutically active agent dissolved or dispersed in a carrier oil or liquid, in an aqueous phase, . . .". Attention is directed to MPEP 2173.05(h). Also, clarification of the end of an alternative group may be made by the insertion of appropriate punctuation, *e.g.*, a semi-colon.

Claim Interpretation

7. Claims 1-10 and 27 are directed to method of preparing dispersions of a hydrophobic pharmaceutical active agent.

Claims 11-23 are directed to corresponding dispersions of hydrophobic pharmaceutical active agent free of dissolved gas and drug delivery systems of said dispersions.

Claims 24-26 are directed to nominal methods of drug delivery.

The claims all employ open transitional language, *i.e.*, "comprising".

Method Claim 10 quantifies the percentage of dissolved gases removed. Method Claim 11 and those dependent thereon (13-14 and 17-25) sets forth a substantially dissolved gas free dispersion. The phrase "substantially free of dissolved gases" is defined as follows (page 19, lines 21-24):

> A dispersion or drug delivery system or component thereof "substantially free of dissolved gases" refers to a dispersion or system or component thereof wherein at least 80% of dissolved gas is removed, more preferably at least 90% or 95%. Most preferably at least 99% of dissolved gasses are removed.

The Claim 11 limitation is interpreted as at least 80% of dissolved gas is removed. Since this is a relative percentage and no reference to the initial dissolved gas is defined, the broadest reasonable interpretation would include an initial upper limit of initial gas dissolved equates to the saturation limit.

Claims 4 and 14 set forth "wherein said dispersion is substantially free of stabilizers, surfactants or dispersants". The phrase "said dispersion is substantially free of stabilizers, surfactants or dispersants" is defined as follows (pages 15 to 16, lines 24 to 3):

> An aspect of the invention thus provides dispersions having significantly less (for example less than about 50% or less than about 20%, more preferably less than about 10%) of what might be typically used in the preparation of dispersion without degassing and are **preferably substantially free of surfactants, stabilizers and dispersants**. Surfactants, (or stabilizers or dispersants) are generally employed in the art in conjunction with carrier oils or liquids, typically 1-5% (v/v) of the hydrophobic liquid phase, which in itself is generally about 1% (v/v) of the aqueous dispersion. Therefore, one embodiment of **the invention provides a dispersion having less than about 0.5-2.5% (w/v) or (v/v)**

of surfactant/stabilizer/dispersant in the hydrophobic phase (solid, liquid or oil). (Emphasis added).

The remaining claims are generic regarding the gas removal step or the amount of gas removed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

9. Claims 1-5, 7-18, 20-22, 24-25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuda et al., 5,650,172. Matsuda et al (column 5, lines 63 et seq; and example 1) disclose formation of an emulsion of a hydrophobic pharmaceutical active agent, *i.e.*, paramethasone palmitate.

The use of deoxidized distilled water was employed in making the emulsion. Deoxidized distilled water is conventionally made by bubbling a gas other than oxygen, *e.g.*, N_2, and is not considered degassing as claimed.

The crude emulsion was allowed to stand under reduced pressure for about 10 to about 20 minutes for deaeration followed by homogenization. The deaeration is removing dissolved gas as claimed. Matsuda et al (column 6, lines 25-63) discloses lyophilizing the emulsions referring to the materials as lipid particles and reconstituting said lyophilized materials.

Lyophilization is also known as freeze drying. Said process includes freezing the emulsion (-25 ^{o}C) followed by drying under reduced pressure. Typical pressures for lyophilizing are measured in microns of mercury or less than a tenth of a mbar. The

claimed processes to removing dissolved gases are deemed to read on the Matsuda et al reference. The concentrations of claim 10 would be expected to be inherent to the Matsuda et al processes.

Matsuda et al (column 6, line 13) discloses the addition of water is for injection.

The composition comprises oleic acid, wherein the process does not disclose neutralization the acid. Said oleic acid would be expected to be an oil component rather than a stabilizer, surfactant or dispersant. The emulsion employs ~ 0.5 % (w/w) yolk lecithine. Applicants' limitation "substantially free of stabilizers, surfactants or dispersants" reads on the Matsuda et al concentrations.

Injection is implicit to the disclosed purpose of adding water. The reconstituted water for injection would have been expected to have been degassed. The interfacial tension of the claims would have been inherent to the otherwise anticipated compositions of the Matsuda et al reference.

10. Claims 1-5, 8-16, 18 and 20-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Borman et al, US 5,536,413. Borman et al (examples) discloses treating DIPRIVAN®[1] to filtration to remove microorganisms and dissolved gas. Borman et al (column 1, lines 23-44) discloses parenteral administration includes injection as well as inhalation, which may function best when inhaled in the form of aerosols. Borman et al clearly contemplates the delivery systems including injection and inhalation. The methods of delivery of claims 24-26 would have been inherent to employing the Borman et al methods and compositions as disclosed and clearly contemplated therein.

11. Claims 1-6, 10-16, 18-19, 22, 24-25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Riess et al, US 5,573,757. Riess et al (examples) disclose the methods and compositions as claimed. Riess et al (example 1) discloses degassing the compositions. Riess et al (examples 1, 14 and 15) discloses composition that are substantially free of stabilizers, surfactants or dispersants.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-6, 10-16, 18-19, 22, 24-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sekins et al, US 5,158,536. Sekins et al (column 9, lines 21-26) discloses forming emulsions of perfluorcarbon liquids as breathable liquids in the

[1] Characterized (column 17, lines 25-29) as a propofol medicament in an oil-in-water emulsion which also

oxygenation of a patient. Sekins et al (column 8, lines 62-68) further discloses the perfluorcarbon liquids are "most preferably substantially (almost totally) degassed".

Sekins et al differs from the claims in an exemplified process as of degassing the perfluorcarbon liquids and making the emulsion.

It would have been obvious to one of ordinary skilled in the art at the time of applicants' invention to substantially degassed the perfluorcarbon liquids and emulsify said liquids as breathable liquids for the advantage of incorporating water soluble therapeutic agents for treating a patient.

15. Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuda et al., 5,650,172, or Riess et al, US 5,573,757, in view of Borman et al, US 5,536,413.

Matsuda et al (column 5, lines 63 et seq; and example 1) disclose formation of an emulsion of a hydrophobic pharmaceutical active agent, *i.e.*, paramethasone palmitate. The crude emulsion was allowed to stand under reduced pressure for about 10 to about 20 minutes for deaeration followed by homogenization. Matsuda et al (column 6, lines 25-63) discloses lyophilizing the emulsions referring to the materials as lipid particles and reconstituting said lyophilized materials. Matsuda et al (column 6, line 13) discloses the compositions are for parenteral injection by the addition of water is specified for injection.

Riess et al (examples) disclose the methods and compositions as claimed. Riess et al (example 1) discloses degassing the compositions. Riess et al (examples 1,

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includes soybean oil, glycerol, lecithin and sodium hydroxide.

14 and 15) discloses composition that are substantially free of stabilizers, surfactants or dispersants and are injectable. Riess et al (column 1, lines 9-14; and column 7, lines 16-39) disclose the compositions may be employed in theapeutic uses and teaches they may include lipophilic (*i.e.*, hydrophobic) drugs.

Borman et al (examples) discloses treating DIPRIVAN®[2] to filtration to remove microorganisms and dissolved gas. Borman et al (column 1, lines 23-44) discloses parenteral administration includes injection as well as inhalation, which may function best when inhaled in the form of aerosols.

To the extent that Matsuda et al or Riess et al differ in the gas removal degree, gas removal of the dispersion, or the type of application method; These differences would have been to one of ordinary skilled in the art at the time of applicants' invention as taught in the combined prior art and for the advantage of the desired removal of gas prior to perenteral administration.

It would have been obvious to one of ordinary skilled in the art at the time of applicants' invention to substantially degassed the dispersion compositions of Matsuda et al or Riess et al by employing the Borman et al device for the advantages of removal of particulates, microorganisms and dissolved gas prior to parenteral administration.

16. Claims 12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garti et al, US 5,847,109. Garti et al (abstract; column 2, line 44 et seq; more particularly columns 2 to 3,lines 67 to 4; column 3, lines 17-22; column 7, lines 6 et seq; Fig. 4; examples and claims) discloses compositions including glucomannans as

stabilizing agents in oil-in-water emulsions that may be employed in making veterinary and pharmaceutical compositions including accepted carriers and diluents.

Garti et al differs from the claims in the disclosure of an exemplified veterinary or pharmaceutical composition as claimed.

Garti et al clearly teaches oil-in-water emulsions having droplet interfacial tensions ranges from 16 to 36 dynes/cm (dynes/cm = mJ/m^2). It would have been obvious to one of ordinary skilled in the art at the time of applicants' invention to employ the systems of Garti et al in making a veterinary and pharmaceutical compositions including accepted carriers and diluents for their implicit veterinary and pharmaceutical advantages.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. See Shinkarenko, column 5, lines 41-49; lyophilizing parameters employing a vacuum of 0.035 mBar. The remaining art cited is cumulative or less pertinent than the prior art relied on herein above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel S. Metzmaier whose telephone number is (571) 272-1089. The examiner can normally be reached on 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David W. Wu can be reached on (571) 272-1114. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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[2] Characterized (column 17, lines 25-29) as a propofol medicament in an oil-in-water emulsion which also

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel S. Metzmaier/
Primary Examiner, Art Unit 1796

DSM

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includes soybean oil, glycerol, lecithin and sodium hydroxide.